Difficult Decisions in Surgery:
An Evidence-Based Approach

Neil Hyman
Konstantin Umanskiy *Editors*

Difficult Decisions in Colorectal Surgery

Springer

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I dedicate this book to my sons EJ and Seth, who have been a never-ending source of pride and joy from the moment they were born, and always the reason for everything.

Neil Hyman

I dedicate this book to my parents Yakov and Eugenia.

Konstantin Umanskiy

Preface

Colon and rectal surgery may very well be on the cusp of a golden age. Our specialty is thriving and our ACGME-approved training programs are extremely popular among the best and brightest general surgery residents. Breathtaking advances in minimally invasive surgery have occurred over the past quarter century including laparoscopic bowel resection, robotic surgery, endoscopic techniques such as endoscopic mucosal/submucosal resection, and transanal approaches such as transanal endoscopic microsurgery and transanal minimally invasive surgery. Innovation in these areas has made surgery safer for many of our patients, enabled sphincter preservation, and reduced the period of disability that many experience after treatment. However, in addition to the obvious benefits of these disruptive technologies, many long-standing questions persist and new ones have been raised.

1. What is the most appropriate use of this new and often more expensive technology? Does the evidence really support the notion that everything new is really better?
2. Considering the primacy of patient safety, how do we decide who should be credentialed to do what?
3. Should *any* surgeon be able to use any technique they wish, irrespective of cost, efficacy, and demonstrated competence?
4. Should these new technologies be evaluated first by a select group of high volume/experienced surgeons in a controlled and measured environment before more widespread adoption?
5. Do we really have adequate hypotheses and frameworks of understanding for the common diseases we treat?
6. Without them, can we really devise rational treatment approaches for these maladies?
7. As such, are almost all our treatments largely empiric and lacking in the basic scientific underpinnings that would move us beyond therapeutic "hail Mary's"?

With this state of affairs, the practice of colon and rectal surgery has largely been driven by expert opinion and the practice of thought leaders – it is often the best we have. In this book, we have put together a select and highly respected group of

leaders in our field and asked them both to critically review the evidence in a controversial area which they have typically contributed to and investigated during their career. We also asked them to supplement this with their clinical insights and personal experience. This is not a comprehensive textbook of colon and rectal surgery which attempts to review the basic anatomy and physiology of the vast spectrum of problems one may encounter in the small intestine, colon, rectum, and anus. Many excellent textbooks like this already exist. Rather, we have selected a broad array of difficult and often controversial problems that the surgeon who deals with colorectal disease often encounters. We asked our experts to imagine that they received a phone call from a busy surgeon in the surgeon's lounge who wanted to know how a particular challenging patient management issue should be handled. The goal was *not* to list every treatment that has ever been described or utilized.

1. What are my best options?
2. What is the best evidence for/against these options in the literature?
3. How do I decide?
4. What do you think and what do you do?

The reader will be able to see what the highest quality evidence available exists to guide our management decisions. However, it will be evident that there is always going to be considerable room for alternative opinions and approaches. A different acknowledged expert with considerable clinical experience and knowledge of the applicable evidence may see things differently and approach the same problem using a very different algorithm. Indeed, as much as we like to talk about evidence-based approaches, the "evidence" for much of what we do is often lacking and meager. We hope that the reader will find real help and a sense of perspective from this book. We particularly hope that we inspire our trainees and junior colleagues to uncover new paradigms of care, contribute high quality evidence to the literature, and advance the scientific underpinnings of our management decisions. Our patients deserve no less!

Chicago, IL, USA Neil Hyman

Acknowledgments

We gratefully acknowledge the talents, expertise, and assistance of Ms. Abby Larson – without her, there would be no book. We also thank Dr. Mark Ferguson for his guidance and leadership and Kumar Athiappan of Springer for his diligence and responsiveness. We also thank our mentors, colleagues, fellows, residents, students, and patients who provide us the inspiration to learn and improve every day.

Contents

Part VIII Technique

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Chapter 1
Introduction

Konstantin Umanskiy

Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?

T.S. Eliot 1934

Tell Me a Story. The Importance of an Anecdote

At the center of medical decision-making is always the patient; their story, their feelings, their family support and their unique perception of the problem. At this intersection of medical art and science stands the surgeon who must combine the unique aspects of the ancient art of healing with modern medical science to provide the treatment most likely to create a good outcome. Instinctively we as surgeons tend to rely on impressions from our clinical practice, experiences during surgical training, or maybe what we have just heard at the morbidity and mortality conference this week. This anecdotal decision making, while typically thought of as rudimentary and not "evidence-based", is in fact one of the most basic forms of evidence based medicine(EBM). This method of medical practice has been known since antiquity where early EBM was based on ancient historical or anecdotal accounts. Teaching during this time was mainly authoritative and passed on with stories. By the seventeenth century, a renaissance era of medical practice had ushered the earliest form of modern EBM. During this period, written journals were kept and textbooks began to become more prominent.

Information Literacy. Learning the New Language

Fast forward to 1970–1990s, the era often called the transitional era of EBM. This time period was characterized by the rise of biomedical informatics, driven by the explosion of published information related to health care. At the same time came

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the advent of the clinical trials and of clinical research, in general. An electronic version of Index Medicus which would ultimately become MEDLINE was expanding rapidly. An early version of what would become a World Wide Web was in advanced phases of development. The stage was set for an entirely new relationship between the world of medical practice, health care and the biomedical literature.

In 1991 the term 'evidence-based medicine' was declared to be both 'a new approach to teaching the practice of medicine' and 'a new paradigm of medical practice'. In 1992, the Journal of the American Medical Association proposed a radical change in the hierarchy of knowledge in which clinical evidence, particularly that stemming from randomized trials and meta-analyses, was placed above the pathophysiological understanding of disease process and 'clinical experience.'[1] This concept, while controversial, took the medical community by storm, fueled by reports such as the one published by Antman et al. [2] that demonstrated that thousands of patients with myocardial infarction had died unnecessarily as a result of failure to adequately summarize the trial evidence on the efficacy of thrombolytic therapy.

With the advent of public access to the Internet via the World Wide Web in 1995, the door had swung open to the proliferation of electronic biomedical resources. But with the rapid explosion of medical information, came the necessity of equipping the practitioners and teachers of medicine with resources to acquire 'information literacy'[3], a concept defined as an identification of the information needed and the process of performing a search, evaluating the quality of the evidence and, finally, integrating it with independent pre-existing information. This process that can be described as 'ask', 'acquire', 'appraise' and 'apply' became the instructional model for EBM [4].

Since the mid-1990's medical journals have featured a number of well-designed analyses and clinical practice guidelines put together by well-respected groups of experts. The number of publications with the keyword 'evidence-based medicine' has risen dramatically from 1984 to 2015 (Fig. 1.1). While the emphasis on evidence-based practice has been robust and quite persistent over the past two decades, the evidence provided often conflicts with other evidence, may be overtly misleading or even just plain wrong. One such conspicuous example was the recent excitement about avoidance of mechanical bowel prep in colon surgery [5], only to later realize that mechanical bowel prep with oral antibiotics as originally proposed by Nichols and Condon decades ago is demonstrably superior [6].

Without a doubt evidence-based medicine provides surgeons with a rational basis to support guidelines for treatment modalities and contributes to standardization of care, which in many instances results in improved quality of care and better patient outcomes. But with the guidelines may come an unwelcomed restrictiveness; many surgeons are reluctant to alter their practice and may have very legitimate concerns whether the generalized evidence really provides the best solution for the individual patient. The interpretation of data as presented in medical literature may require the reader to become 'information literate' to appraise the quality of the evidence and its true applicability to the individual surgeon's practice.

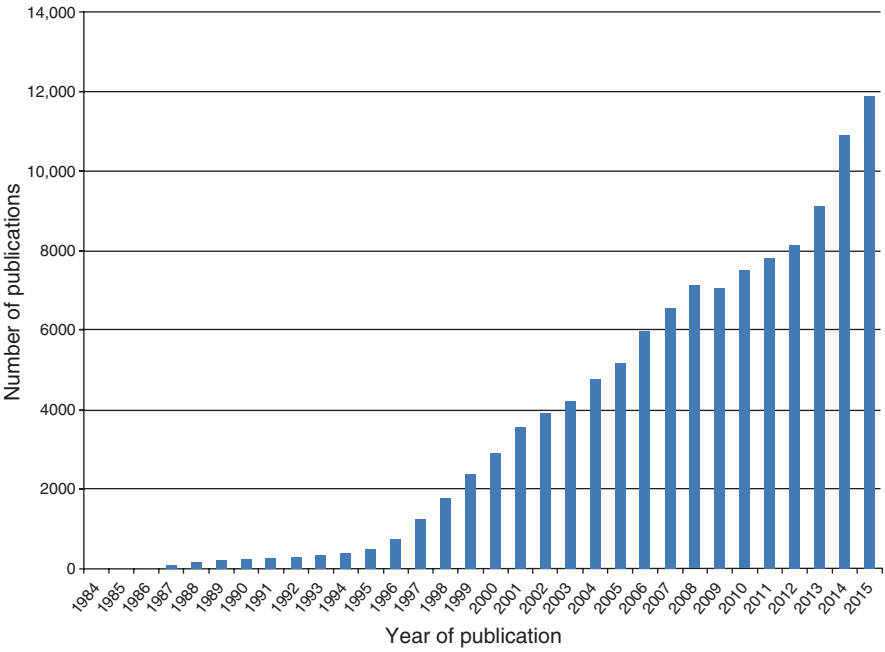

Fig. 1.1 PubMed entries with keywords 'evidence based medicine'

Introduction of new technology into colon and rectal surgical practice is resulting in a rapidly expanding technical armamentarium. Some surgeons self-described as "early adaptors" are quick to jump on the bandwagon to embrace new and often unproven technology, driven by a general desire to advance the field and push the envelope. An unbiased and thoughtful review of data and careful reflection on the ethical considerations based on the surgical dictum of "do no harm" should be liberally exercised.

Bringing It Together

Initially, EBM focused primarily on determining the best evidence and applying that evidence to the clinical situation at hand. This early approach lacked emphasis on traditional aspects of clinical decision-making such as physiologic rationale and individual clinical experience. Fortunately, with evolution of EBM came the realization that research-based evidence alone may not be an adequate guide to action. Instead, clinicians must combine their experience, the applicable scientific evidence and the patient's wishes and values before making a treatment recommendation. Figure 1.2 depicts a model for evidence-based decisions, which emphasizes "clinical expertise" as an overarching component in EBM decision-making. Clinical

Fig. 1.2 Current model of evidence-based clinical decision making (Adapted from: Haynes et al. [9])

expertise encompasses the patient's clinical state and surrounding circumstances, combining it with relevant research evidence, and the patient's preferences. Getting the diagnosis and prognosis right and knowing how to provide treatment demand more skill now than ever before because the options are many and patient expectations are high. Surgeons in the current clinical environment must be abreast of not only the scientific evidence; they must also acquire and hone skills needed to both interpret the evidence and apply it appropriately in clinical settings. Finally, and very importantly, the patients' goals, values and wishes remain the cornerstone to the best and informed decisions [7].

Why This Book?

How do we know that a parachute works? Well, one can say we don't know. Apparently there has never been a randomized, double blind, prospective, placebo-controlled trial assessing the efficacy of the parachute [8].

Sometimes common sense is all that is needed, and medicine in this regard is no exception. This book was conceived as an opportunity to hear the voice of a no-nonsense, wise mentor, who can build on the available evidence, put it in perspective and provide practical advice to tough clinical problems. While not all encompassing, this book has been designed to help surgeons with their decision-making on a very practical level based on the best available evidence. We asked many of the most 'information literate' experts in the field of colon and rectal surgery to comb through the evidence, evaluate and summarize it for our readers and provide their opinion and recommendation based on the years of experience caring for patients with com-

plex colon and rectal disorders. We are sincerely grateful to a wonderful group of colleagues and friends, recognized experts in the field of colon and rectal surgery, for their contributions to this book.

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Chapter 2
Evaluating Evidence

W. Donald Buie

Introduction

Evidence can be defined in the broadest sense as "… any empirical observation, whether systematically collected or not" [1]. Clinical evidence can include everything from the unsystematic observations of the individual clinician, physiologic experiments in animal models or the systematic observation of clinical events. Due to this wide variety of sources, it is of varying quality and applicability. How confident are we in the stated results? How accurate are the estimates of effect? Can the results be generalized to my patient? Evidence based decisions require not only the identification of all relevant evidence for a specified outcome but a systematic evaluation of the evidence such that *best* available evidence is used to support good clinical decisions.

Throughout this book, the quality of evidence and in turn the strength of the recommendations that follow is based primarily on GRADE (Grading of Recommendations Assessment, Development and Evaluation) [2]. GRADE is a transparent, structured, reproducible system for reviewing and evaluating medical evidence for any specified outcome. In its basic form, it can be used by a clinician to help identify the best treatment course for a specific clinical situation, and in its complete form by guideline developers to assess the literature on a broad topic to produce clinical practice guidelines (CPGs) on important patient specific outcomes [2]. This chapter will briefly outline the steps that are required to apply GRADE when evaluating evidence for specific clinical decisions. It will summarize the process of evaluating evidence by exploring stratification by study design, assessing random error and bias, identifying methodological limitations and assessing

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confidence in the measured effect. For a complete review of the GRADE system clinicians are encouraged to read a series of articles from the British Medical Journal [3–5] or a more recent series from the Journal of Clinical Epidemiology designed for guideline developers [2, 6–13]. The ideas and concepts in this chapter are summarized primarily from the latter series and the reader is encouraged to seek out these references for a more in depth discussion.

Initial Evaluation

Evaluation of evidence begins with a well-constructed clinical question including a specified population, a specific intervention, a comparator and specific outcomes, a process often abbreviated as PICO [14] (Fig. 2.1). A poorly designed question negatively affects the appropriateness of the collected evidence and in turn the evaluation of that evidence. With the ever increasing volume of evidence present in the medical literature and the constant turnover of best evidence, it is difficult for the clinician with limited time and resources to keep up to date. This has fuelled an explosion in structured reviews and CPGs that aim to summarize the literature in a structured and transparent fashion. Not all subjects are covered with a CPG and thus the clinician must be able to formulate an appropriate search and evaluate the literature independently.

Once a literature review is complete, each individual study must be vetted for its relevance to the topic. Does it address the outcomes of interest? Does it apply to the particular practice setting? Does it apply to the particular patient population? Not all studies will address all outcomes. However, the evidence for all important patient outcomes in a specific clinical situation must be evaluated. For example, in Stage IV rectal cancer when considering a palliative resection versus long-term chemotherapy, evidence for each management strategy must be evaluated for both quality and quantity of life. In addition the risk of a poor outcome *as viewed by the patient* due to either surgical or medical complications must be considered. For many questions a structured review or CPG exists that covers most of the outcomes of interest but a primary literature search may be required to supplement evidence for specific outcomes.

Stratifying Evidence

Once the evidence is collected, it is initially stratified by study methodology. Well designed structured reviews and meta-analysis based on well-designed RCTs are the highest order of evidence, followed by well designed RCTs themselves, lower quality RCT studies with methodological limitations and finally observational studies (cohort and case control). Within the GRADE system, expert opinion is not viewed as evidence in and of itself. In other words, while an expert is required to interpret evidence, expert opinion may or may not be based on best evidence.

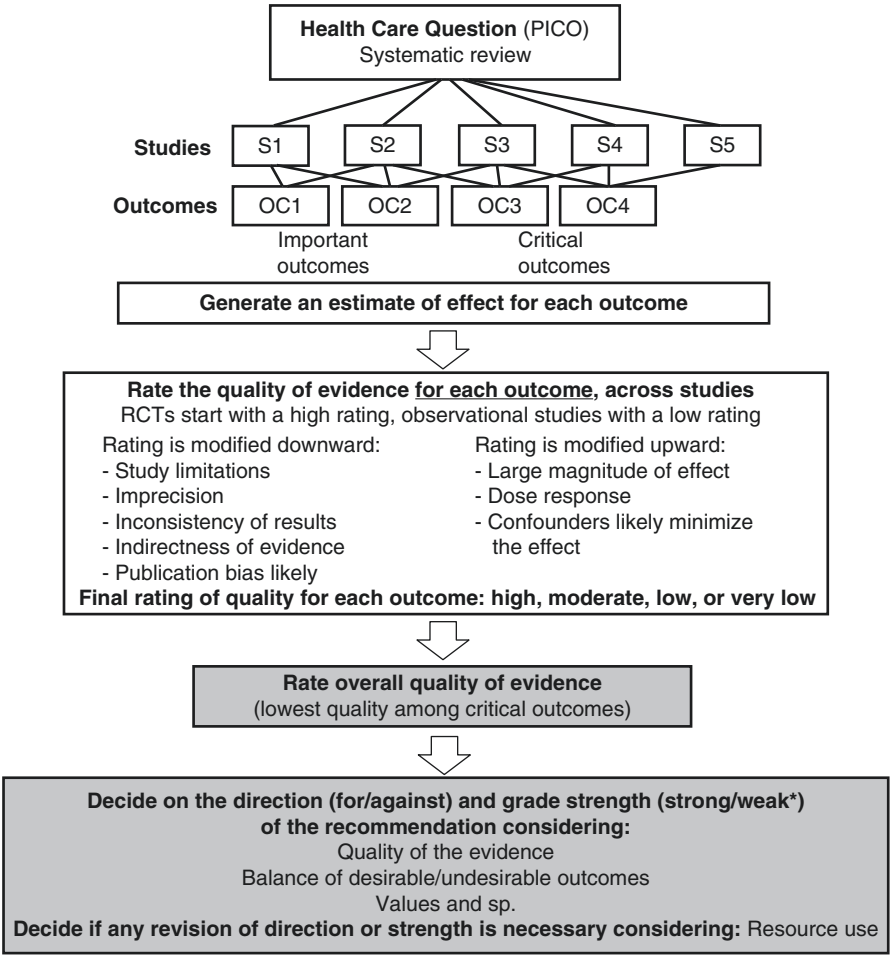

Fig. 2.1 The GRADE process for developing recommendations (Adapted from Guyatt et al. [2])

Random Error and Systematic Error (Bias)

All studies are subject to error, which may to a greater or lesser extent affect the results of a study and our confidence in the stated results. Error can be classified into two major categories: random error and systematic error or bias. Random error is the variation in outcomes due to chance alone. Studies are performed on sample populations from the population at large, thus the results of each study are estimates of the actual effect of an experimental intervention on the overall population. If a study is performed on 20 different sample populations replicating strict methodology each time, the final results of each trial will be closely approximated but will vary due to chance, much like a coin toss performed multiple times will not always add up to

exactly 50% heads and 50% tails. Random error is by definition variable and can occur in either direction, (you can toss 7 heads or 6 tails in a row), resulting in a positive or negative effect on the estimate of an outcome of interest. It can be minimized through the use of large sample sizes either in individual studies or by combining similar smaller studies in a meta-analysis. A well designed prospective study should have a sample size calculation for a specific outcome as part of its methodology.

Systematic error or bias results in a systematic or fixed effect on a study. This type of error is not affected by sample size as it is related to study methodology. Virtually no study is devoid of all bias. However, when evaluating a study one must try to determine whether the effect from systematic error or bias is large enough to significantly alter the observed effect of an experimental intervention.

Methodological Limitations (Bias)

There are four levels of evidence in the GRADE system; high quality, moderate quality, low quality and very low quality (Table 2.1) [7]. Evidence from RCTs starts out as high quality evidence but may be down graded to moderate or even low quality if bias or methodological issues are identified. Similarly, although evidence from observational trials is generally classified as low or very low quality, it may be upgraded under certain circumstances (Fig. 2.1).

Bias in randomized trials can occur in three parts of a study; differences observed at the start of a study, differences that arise as a study progresses and differences at the completion of a study [16] (Table 2.2). Blinding should be present at all levels of a trial starting with allocation and randomization, and including the patient, the care giver, the assessors and the data analysts. When absent, the results usually favor an overestimation of effect. Differences in treatment or exposure to confounding treatments in the experimental arm, incomplete follow up or loss to follow up and failure to adhere to the intention to treat principle in superiority trials are also associated with over estimation of effect. Loss to follow up takes on greater importance when the number of events in either the experimental or control group is small relative to the percentage lost to follow up or if the loss to follow up is imbalanced between the two groups.

Studies that investigate treatment with *observational* design are inherently subject to bias. While the investigator does not have any control over these biases, the clinician should look for statistical adjustments or the use of hard endpoints by the investigator. The clinician must evaluate whether the observed biases could potentially account for an observed treatment effect [16].

Although study design is important, GRADE applies to each specific outcome within a study. Bias may affect specific outcomes within the same study to a greater or lesser degree increasing or reducing our confidence in each observed outcome. For example lack of blinding of assessors may not affect the assessment of a post-operative outcome such as death but may be responsible for bias in the assessment of a wound infection.

Table 2.1 GRADE: levels of evidence and definitions

Category	Definition	Examples
High	We are very confident that the true effect lies close to that of the estimate of the effect	Randomized trials without serious limitations
		Well performed observational studies with very large effects
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Randomized trials with serious limitations
		Well-performed observational studies yielding large effects
Low	Our confidence in the effect estimated is limited: the true effect may be substantially different from the estimate of the effect	Randomized trials with very serious limitations
		Observational studies without special strengths or important limitations
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimated of effect	Randomized trials with very serious limitations and inconsistent results
		Observational studies with serious limitations
		Unsystematic clinical observations (case series or case reports)

Adapted from Balshem et al. [7]

Table 2.2 Study limitations in randomized trials

1. Lack of allocation concealment
Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (e.g., "pseudo" randomized trials with allocation by day of the week, birth date, chart number etc.)
2. Lack of blinding
Patient, care givers, those recording outcomes, those adjudicating outcomes or data analysts are aware of which arm patients are allocated
3. Incomplete accounting of patients and outcome events
Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up and failure to conduct both analysis considering only those who adhered to treatment, and all patients for whom outcome data are available
4. Selective outcome reporting bias
Incomplete or absent reporting of some outcomes and not others on the basis of results
5. Other limitations
Stopping early for benefit
Use of unvalidated outcome measures (e.g. patient reported outcomes)
Carryover effects in crossover trial
Recruitment bias in cluster randomized trials

Adapted from Balshem et al. [7]

Confidence in Effect

Downgrading Evidence

A study may be well designed with minimal bias yet we may lack confidence in the degree to which the experimental effect is demonstrated. In other words, is the treatment really as good as the results suggest? In GRADE there are four additional qualities that must be evaluated for each specific outcome which when present will downgrade the evidence from a RCT either one or two categories depending on how serious the shortcomings are (Fig. 2.2)

Imprecision

Imprecision refers to the accuracy of the point estimation of effect. It is most easily identified by examining the 95 % confidence interval (CI) around the difference in effect; the larger the interval the less precise the estimate [10]. Examine the absolute and not the relative difference as the latter will inflate any observed effect. Use a theoretic test: if the true value was equal to the upper or lower 95 % CI and if this result would change the course of action, then consider the results imprecise and downgrade the evidence [10]. Be suspicious when the effect is large, yet both the sample size and the number of events are small even if the CIs are narrow; in other words, relatively few patients with relatively few incidents should call a large magnitude of effect into question.

Inconsistency

When the results of several well conducted RCT vary widely with respect to a specific outcome the evidence is inconsistent [11]. An attempt should be made to

A summary of GRADE's approach to rating quality of evidence

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomized trials	High ⇒	Risk of Bias –1 Serious –2 Very serious Inconsistency –1 Serious –2 Very serious Indirectness –1 Serious –2 Very serious Imprecision –1 Serious –2 Very serious Publication bias –1 Likely –2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	High (four plus: ⊕⊕⊕⊕) Moderate (three plus: ⊕⊕⊕◯) Low (two plus: ⊕⊕◯◯) Very low (one plus: ⊕◯◯◯)
Observational studies	Low ⇒			

Fig. 2.2 A summary of GRADE's approach to rating quality of evidence (Adapted from Balshem et al. [7])

explain the variability between studies based on differences in populations, interventions, outcome measurement or other methodologic issues. Subgroup and sensitivity analysis may be necessary to illuminate these differences which may or may not downgrade the evidence based on the perceived effect on the outcome of interest.

Indirectness

There are two types of indirectness recognized within the GRADE system [12]. The first is when there is evidence comparing intervention A with intervention B and intervention B with C but no direct evidence from a comparison of A with C. In this case an inference can be made but the level of evidence for that outcome is marked down one level. This type of indirectness is more common in pharmacologic trials. Evidence may also be classified as indirect if there are differences between the best available evidence with respect to the populations under study, specific interventions, co-interventions or outcome measurements and the PICO (population, intervention, comparator and outcome) of the initial clinical question.

Publication Bias

Negative studies are less likely to be published resulting in publication bias [9]. These studies also suffer from lag time bias being published at a later date. Negative studies are often relegated to lower impact journals or as a thesis or abstract in an obscure publication such as proceedings of a meeting and in languages other than English. Omission of negative studies may lead to an overestimation of treatment effect.

Another form of publication bias is selective outcome reporting [9]. This should be suspected if some of the expected outcomes for a specific clinical problem are suspiciously absent. Selective outcome reporting may also occur when composite or derived outcomes are reported as significant and primary outcomes are either not significant or not discussed. It also causes an overestimation of the effects of an intervention.

Upgrading Evidence

Occasionally outcomes from descriptive or observational studies which are normally classified as low level evidence may be upgraded one level. GRADE has specified three situations whereby observational evidence may be upgraded usually from very low to low level evidence (Fig. 2.2).

Large Magnitude of Effect

Occasionally an observational study demonstrates a very large treatment effect [13]. GRADE defines a large effect as a relative risk (RR) of >2.0 and <5.0 based on consistent evidence from at least two studies with no significant confounders. A very large magnitude of effect is defined as a relative risk of >5.0 and <0.2. The effect should be based on direct evidence with no other perceived forms of bias. An example of this would be the original case series published on mesorectal excision where the reduction in local recurrence was far greater than either accepted levels in the literature following standard surgery at the time or the improvements obtained by adjuvant therapy [15].

Plausible Confounders

In this situation, a confounder effect would be expected to act in opposition to the observed effect [13]. For example, all plausible confounders would reduce the demonstrated effect or increase it if no effect was observed. Thus the presence of the confounder increases the likelihood that the observed effect is real and therefore the evidence may be upgraded.

Dose Response Gradient

When increased exposure to an intervention is associated with a larger treatment effect or greater harm, this may be considered a dose response gradient [13]. In this situation, the evidence may be upgraded as we have more confidence in the observed effect. This is not likely to occur in surgical studies as the treatment effect is usually an all or none phenomena.

Overall Quality Rating

Once the evidence for each outcome has been identified, stratified and evaluated for the presence of bias, an estimation of the confidence in the observed effect is determined based on the qualities in the previous section. This information is best summarized in an evidence profile table (EP) [2]. Next, a *quality rating* of the best available evidence is assigned for each separate outcome to one of the four categories (Table 2.1). This becomes the overall estimate of the confidence in the expressed treatment effect for a specific outcome [16]. Prior to a recommendation, an overall quality rating for all the evidence for all outcomes is determined. When there are

different levels of quality for each outcome, the GRADE system by convention bases the overall quality rating on the lowest quality of available evidence for the specified outcomes (Fig. 2.2).

The overall quality rating is the basis for the strength of any recommendations that follows (Fig. 2.1). Strength of recommendation is defined as "the extent to which we can be … confident that desirable consequences of an intervention outweigh undesirable consequences" [16]. GRADE classifies recommendations into two categories based on how strongly the evidence supports the recommendation. A strong recommendation indicates that a specific course of action would be appropriate for most patients in most situations. A weak recommendation on the other hand indicates that although the recommended course of action would be appropriate for most patients in this situation, for many patients it would not [17]. Occasionally evidence for a specific outcome is so inadequate that no evidence based recommendation can be made.

Conclusion

Clinical decisions must be based on best evidence. High quality structured reviews or CPGs with transparent evaluation of quality of the evidence using a system such as GRADE are invaluable. While the clinician may not have the time or training to perform a structured review, they must be able to evaluate studies for quality when information on a desired outcome is not part of a CPG.

While evidence is essential for good clinical decision-making, it cannot be applied in isolation. A clinician must consider the risks versus benefits and the burdens and costs of each management strategy. In addition, the goals, values and expectations of the patient as well as the experience of the clinician in similar situations must be considered. It is the responsibility of the clinician to assess and interpret the evidence as it applies to each individual patient's situation and guide the patient in the quest for optimal, safe, patient centered care.

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Part I
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